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Regularity of Respiratory Waveform Depends on Ventilation Parameters

東京有明医療大学大学院

保健医療学研究科

保健医療学専攻

柔道整復学分野

学籍番号：5217001

氏　　名：宮下拓麻

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Takuma Miyashita[1], Koki Takahashi[2], Chihiro Edamatsu[3], Ikuo Homma[2]

[1] Graduate School of Health Sciences, Tokyo Ariake University of Medical and Health Sciences.

[2] Tokyo Ariake University of Medical and Health Sciences.

[3] Kurashiki University of Science and the Arts.

Abstract

Entropy is a nonlinear method for quantifying the regularity and order of a system. Entropy was originally born from thermodynamics and is now used in various fields, such as statistical mechanics and information ethics. Approximate Entropy (ApEn) is an index that has been developed to quantify the complexity of data over time. This study aimed to use ApEn measurement to clarify the relationship between the regularity of the respiratory waveform and ventilation parameters for humans in a resting state. The 5 minutes resting respiratory metabolism of thirteen healthy participants was measured, including respiratory rate (RR), tidal volume (V_T), minute ventilation ($\dot{V}_E$), end-tidal oxygen concentration (E_TO_2), end-tidal carbon dioxide concentration (E_TCO_2), end-tidal carbon dioxide tension ($P_{ET}CO_2$), inspiration time (T_I), expiration time (T_E), and respiration time (T_{TOT}), and the ventilatory response to end-tidal carbon dioxide tension ($\dot{V}_E$ /$P_{ET}CO_2$) was calculated. ApEn values and ventilation parameters were examined using Pearson's product-moment correlation coefficient. The ApEn value of the respiratory waveforms of participants was 0.291 ±0.050 (mean ±SD); these values were positively correlated with T_I, T_E, T_{TOT}, E_TO_2, and $P_{ET}CO2$, and negatively correlated with RR, E_TCO_2, and $\dot{V}_E$/$P_{ET}CO_2$. There were no correlations with V_T or $\dot{V}_E$. The results revealed a correlation between ApEn values and RR, T_I, T_E, and T_{TOT}. The respiratory waveform of a person with fast respiration and a high respiration rate was regular. The correlation between the regularity of the respiratory waveform and $P_{ET}CO_2$ and $\dot{V}_E$/$P_{ET}CO_2$ showed that those with regular respiratory waveforms had increased sensitivity to CO_2 and were in a respiratory state close to hyperventilation. Those with regular respiratory waveforms at rest may have unconsciously felt breathless due to anxiety. The fact that no correlation was observed between V_T and $\dot{V}_E$ supports the notion that the regularity of the respiratory waveform is not determined by ventilation volume but by respiration rate.

keywords: respiratory waveform, regularity, Approximate Entropy, hyperventilation

Ⅰ. Introduction

Breathing is an important behavior in life-sustaining activities and is performed by an individual approximately 20,000 times a day. It is widely known that the main function of respiration is to inhale oxygen and exhale carbon dioxide to sustain life. This life-sustaining respiration, called metabolic respiration, is governed by the respiratory center in the medulla and pons of the brainstem. However, in addition to metabolic respiration, behavioral respiration occurs in response to activity in the upper center of the brain[1,2). Behavioral respiration, unlike metabolic respiration, is respiration that can vary voluntarily, such as during pronunciation and deep breathing. Furthermore, in recent years, reports of emotional breathing affected by various emotions out of this action of breathing have been made[2]. The center of emotional respiration is in the limbic amygdala[3,4] and responds to emotional changes such as happiness, sadness, and fear. In other words, respiration is generated and maintained by metabolic respiration that mainly maintains homeostasis, as well as behavioral respiration that can be intentionally fluctuated and emotional respiration that responds to changes in emotions, and always undergoes complex fluctuations.

It is known that time-series data of biological signals fluctuate due to various factors. Considering the characteristics of such time-series data, as it is difficult to determine the average or standard deviation of the data, it is desirable to use a nonlinear approach [5]. Entropy is a nonlinear method for quantifying the regularity and order of a system. Entropy was originally born from thermodynamics and is now used in various fields such as statistical mechanics and information ethics. Approximate Entropy (ApEn) is an index that has been developed to quantify the complexity of data over time, and it was adapted to the clinical physiology field and to heart rate data by Pincus[5]. ApEn research reports were used by Pincus et al.[6]. They showed that although heart rates of deceased infants with Sudden Infant Death Syndrome were within a normal range, their rates were less variable than that of healthy infants, and thus, they reported that SIDS had some relation to heart rate variability by means of ApEn. Ryan et al.[7] report that heart rate variability becomes regular with age, and it is more regular in men than women. Shin et al.[8] used ApEn to determine that changes in heart rate variability and atrial fibrillation precede spontaneous seizures. According to these reports, it is clear that ApEn is a method that can be used to quantify the regularity of heart rate variability, and that heart rate variability changes regularly with disease and aging. Respiration is a complex biological signal similar to heart rate variability. Therefore, we believe that it is also possible to evaluate the regularity of the respiratory waveform using ApEn. However, few reports have used ApEn for respiratory analysis, and it is not clear if there is regularity in the respiratory waveform. We performed measurements in healthy adults to clarify whether regular respiratory waveforms have regularity in a resting state and how they relate to ventilation parameters.

Ⅱ. Materials and Methods

1) Participants

Thirteen healthy participants (8 males) aged from 20 to 22 years were included in this study. None of the participants had any psychiatric, neurological, or pulmonary disorders. The mean age ±SD was 21.0 ±0.7 years, height was 163.1 ±8.4 cm, and weight was 57.1 ±11.6 kg. All participants provided written informed consent, and the study was approved by the Ethics Committee of Tokyo Ariake University of Medical and Health Sciences (Approval number: Tokyo Ariake University of Medical and Health Sciences Ethics Approval No. 287).

2) Methods

(1) Measurement of respiratory metabolism

In the sitting position, each participant's respiratory metabolism was measured for 5 minutes using a facemask connected to a respiratory monitor (AE-100i, Minato Medical; Osaka, Japan). The room temperature was maintained at 26.8 ±0.7 °C. After the participants remained quiet, respiratory rate (RR), tidal volume (V_T), minute ventilation ($\dot{V}_E$), end-tidal oxygen concentration (E_TO_2), end-tidal carbon dioxide concentration (E_TCO_2), end-tidal carbon dioxide tension ($P_{ET}CO_2$), inspiration time (T_I), expiration time (T_E) and respiration time (T_{TOT}) were measured breath by breath for 5 minute. $\dot{V}_E/P_{ET}CO_2$ was calculated as a ventilatory response to end-tidal carbon dioxide tension. All respiratory data were stored on a laptop computer. The data obtained from the respiratory monitor were analyzed for the average value for 5 minutes of measurement.

(2) Acquisition of Respiratory Waveforms

Flow waveforms from a respiratory monitor were inputted to a laptop computer via an A/D converter (PowerLab, ADInstruments; Sydney, Australia) and recorded by analysis software (LabChart7, ADInstruments). Of the recorded 5-minute flow waveforms, 10 waveforms free of artifacts such as body motion were arbitrarily selected from 5 locations, and the ApEn of each was calculated. The average value of ApEn at the five locations was used for analysis.

(3) Calculation of ApEn value

ApEn is affected by the number of waveforms and the number of data included in the time-series data, and so when calculating it is necessary to complete the number of waveforms and the number of data among the selected data [9]. Therefore, in this study, the number of waveforms was set to flow waveforms for 10 breaths, and the number of data was re-sampled to 1500 using cubic spline interpolation in MATLAB7 (MathWorks; Natick, MA) to unify the number of data. When calculating ApEn values, it is necessary to set m, which determines the vector space, and r, which plays a role in reducing the effects of noise. In this study, we set m = 2 and r = 0.15SD based on the report of Abe et al.[9]. The formula for calculating the ApEn value is shown below.

$$ApEn(m, r, N) = \phi(m, r, N) - \phi(m + 1, r, N)$$

The lower limit of the ApEn value is 0, the ApEn value of regular time-series data such as a sine curve shows a value close to 0, and conversely, random time-series data without regularity shows a high value. In the setting of ApEn value calculation in this study, the ApEn value of a sine curve (0.25 Hz) was 0.181, and the ApEn value of a uniform random number created by spreadsheet software (Microsoft Office Excel, Microsoft; Redmond, WA) was 1.360 (Fig. 1).

(4) Data Analysis

The measured data were expressed as mean ±standard deviation. All statistical analyses were performed with a commercially available statistical package (JMP Pro14.2.0, SAS Institute; Cary, NC). The relationship between the ApEn value of the respiratory waveform and each ventilation parameter was examined using Pearson's product-moment correlation coefficient. A *p*-value of < 0.05 was considered statistically significant.

Ⅲ. Results

The ApEn value of participants' respiratory waveforms was 0.291 ±0.050. The mean values for each of the ventilation parameters are shown in Table 1.

1) Relationship to Respiratory Rate

There was a negative correlation between ApEn values and RR of the respiratory waveform (Fig. 2-A). A positive correlation was observed with T_I, T_E, and T_{TOT} (Fig. 2-B, C, D). Short breathing time in a participant's respiratory rate often indicated a regular respiratory waveform.

2) Relationship to Ventilation

No significant correlation was found between the ApEn value of respiratory waveforms and V_T and $\dot{V}_E$ (Fig. 3).

3) Relationship with End-Tidal Gas Concentration

ApEn values and E_TO_2 showed a negative correlation; ApEn values and E_TCO_2 and $P_{ET}CO_2$ showed positive correlations (Fig. 4). A high E_TO_2 concentration with a low CO_2 concentration indicated that there was strong regularity in the respiratory waveform.

4) Relationship with Ventilatory Response to End-Tidal Carbon Dioxide Tension

ApEn values and $P_{ET}CO_2$ showed a positive correlation; ApEn values and $\dot{V}_E/P_{ET}CO_2$ showed a negative correlation (Fig. 5). This indicates that those who are sensitive to CO_2 have higher respiratory waveform regularity.

Ⅳ. Discussion

1) ApEn Value of a Respiratory Waveform

The average ApEn value of the participants' respiratory waveforms was 0.291 ±0.050. Since the ApEn value varies depending on calculation settings, there are relative differences between the obtained data and, as such, this value is not considered to be the absolute value of the regularity[9)]. The respiratory waveform obtained in this study was more disordered than the sine curve (0.181) and more regular than the uniform random number (1.360), indicating that the respiratory waveform had some regularity. The regularity of heart rate variability has been reported to become more regular with aging[6,7)]. It has been reported that the heart rate variability coefficient decreases linearly as the autonomic nervous activity decreases with aging[10)]. When the time-series data of the biological response shows a regular appearance, this may represent a unique state that is not easily affected by disturbance, and a highly regular respiratory waveform is considered to be a breathing state that is not easily affected by disturbance.

2) Regularity of Respiratory Waveform, Respiratory Rate, and End-Tidal Gas Concentration

The main findings obtained in this study were that those with high respiratory rates had low ApEn values, while those with low respiratory rates had high ApEn values. This means that the breathing waveform of a person with a high respiration rate is regular. When the respiration rate is high, the respiration time is short, and when the respiration rate is low, the respiration time is long. If the minute ventilation is constant, the respiration rate is high, and the respiration time is short, it means that the tidal volume is low. If the minute ventilation is constant and the tidal volume is small, the proportion of dead space occupied by each tidal volume increases and the alveolar ventilation volume decreases. Oxygen that is not involved in gas exchange increases at the end of expiration due to increased dead space volume. In other words, in this study, high end-tidal O_2 concentrations and low end-tidal CO_2 concentrations of participants in this study were caused by tachypnea. The regularity of the respiratory waveform was not correlative with minute ventilation, tidal volume statistically. From this, it became clear that the influence of the respiratory waveform on respiration rate and time was strong.

3) Regularity of Respiratory Waveform and Ventilatory Response to End-Tidal Carbon Dioxide Tension

$P_{ET}CO_2$ and arterial blood carbon dioxide partial pressure are very similar, so $P_{ET}CO_2$ is used as a parameter to estimate arterial blood carbon dioxide partial pressure. An increase in $P_{ET}CO_2$ indicates hypoventilation, and a decrease in $P_{ET}CO_2$ indicates hyperventilation. Since the respiratory waveform of a person with a low $P_{ET}CO_2$ value was regular, it is suggested that the respiratory waveform may be regular while breathing state was close to hyperventilation in this study. $\dot{V}_E/ P_{ET}CO_2$ is an index which indicates sensitivity to CO_2 in the respiratory center. Itakura et al.[11] examined $\dot{V}_E/P_{ET}CO_2$ in patients with hyperventilation syndrome using closed-circuit rebreathing. He reported that healthy subjects had a high $\dot{V}_E/P_{ET}CO_2$ value. He also reported that patients with hyperventilation syndrome increased their respiratory rate rather than tidal volume during CO_2 rebreathing. We revealed that the respiratory waveform was regular in the participants whose $\dot{V}_E/P_{ET}CO_2$ value was high and who were sensitive to CO_2. In general, hyperventilation syndrome, also called anxiety-related dyspnea and tachypnea, and ventilation attacks caused by anxiety, cause decreased arterial blood carbon dioxide partial pressure, respiratory alkalosis due to an increase in pH, and increased sympathetic nervous function. Hyperventilation leads to a gradual respiratory change in excessively stressful situations. To breathe more air, breathing becomes faster which leads to a stuffy sensation in the air passages as if the intake of enough air is not allowed. The resulting physical symptoms include numbness and increased anxiety, turning into a vicious cycle of hyperventilation. In other words, hyperventilation and anxiety are considered to be closely related. In this study, participants with very regular respiratory waveforms may have unconsciously felt stuffy or anxious because they had a high respiratory rate, increased CO_2 sensitivity, and were breathing close to hyperventilation.

4) Relationship Between Breathing and Anxiety

Regarding individual anxiety and respiratory rates, Kato et al.[12] reported that those with an increased respiratory rate in a resting state had high levels of anxiety. The amygdala is the emotional respiratory center which increases the respiratory rate due to anxiety, which is a respiratory control mechanisms[3,4]. It is well known that patients with hyperventilation syndrome or panic disorder have high levels of anxiety, increased respiratory frequency, and persistent decreases in arterial and alveolar CO_2 concentrations[13]. In this study, we also observed that participants with high respiratory rates whose breathing was close to a hyperventilation state had low ApEn values. This suggests that those with a negative emotional state may have increased respiratory waveform regularity due to emotional respiration. Higher regularity (more stability in the pattern of breaths taken) can lead to rhythmic breathing and may prevent the loss of energy for breathing. However, shallow and fast breathing increases dead space and decreases alveolar ventilation, which is inefficient ventilation from the viewpoint of substantial ventilation efficiency. For example, during exercise, the respiratory rate increases with the operation time and load and the dead space ventilation rate decreases, thereby decreasing the dead space ventilation rate (dead space volume / tidal volume)[14]. Also, when performing continuous exercises, such as walking, running, or cycling at a constant rate, the respiratory rate and respiratory cycle are affected by the exercise cycle, and the synchronization of exercise rhythm and respiratory rhythm (Locomotor Respiratory Coupling: LRC) is known to occur[15,16]. This LRC has effects such as a decrease in oxygen intake[17] and a reduction in dyspnea[18] because an increase in respiratory rate is important for improving ventilation efficiency during exercise. For these respiratory responses during exercise, an increase in respiratory rate is appropriate, but in this study, the measurements were done while the participants were at rest. People whose respiration rate is high at rest may try to breathe well with good ventilation efficiency while the regularity of their respiration waveform increases due to an unconscious feeling of breathlessness and to preventing energy loss in breathing.

These findings suggest that the regularity of the respiratory waveform may be related to the respiratory rate and end-tidal gas concentration. Moreover, it is suggested that breathing with a sense of annoyance or anxiety at rest could result in breathing with high regularity of the waveform, or rhythmic breathing that is hardly affected by disturbance.

Ⅴ. Conclusions

The ventilation parameters and the regularity of the respiratory waveform in a resting breathing state of thirteen participants were examined. The results showed that the respiratory rate and respiratory waveform regularity are closely related. This suggests that the regularity of the respiratory waveform may increase as the respiratory rate increases and with a hyperventilation state.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

VI. References

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Table 1. Subject's respiratory parameters

Parameter	Mean	±	SD
RR (BPM)	15.60	±	3.02
V_T (mL)	471.51	±	81.30
$\dot{V}_E$ (L)	7.11	±	1.22
EtO_2 (%)	14.45	±	0.81
$EtCO_2$ (%)	5.39	±	0.50
$P_{ET}CO_2$ (Torr)	38.30	±	3.53
T_I (Sec)	1.60	±	0.34
T_E (Sec)	2.46	±	0.48
T_{TOT} (Sec)	4.06	±	0.77
$\dot{V}_E/P_{ET}CO_2$ (L/Torr)	1.56	±	0.21

Values are mean ± SD

RR, respiratory rate per minute; V_T, tidal volume; $\dot{V}_E$, minute ventilation; E_TO_2, end-tidal oxygen; E_TCO_2, end-tidal carbon dioxide; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; T_I, inspiratory time; T_E, expiratory time; T_{TOT}, total respiratory time; $\dot{V}_E/P_{ET}CO_2$, ventilatory response to end-tidal carbon dioxide tension.

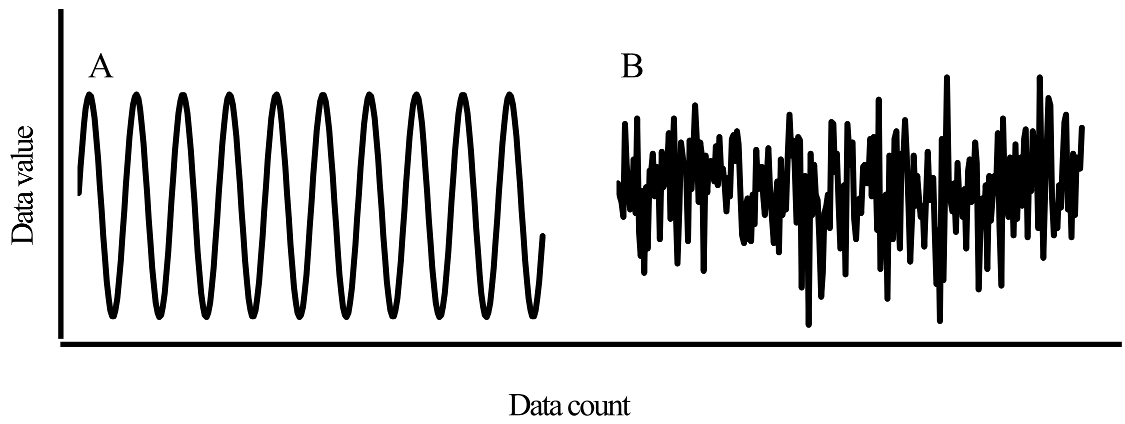

Fig1. ApEn value of Sine wave(A) and uniform random number data(B).
ApEn value of sine wave was 0.181 and uniform random number sata was 1.360.

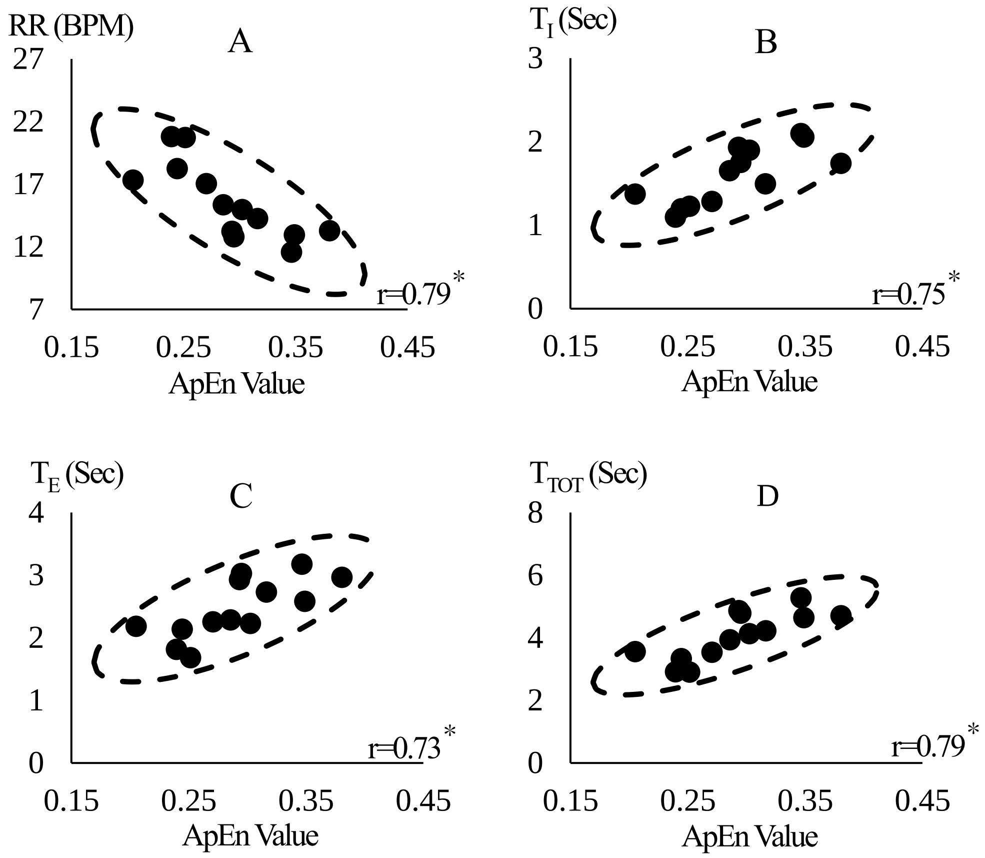

Fig.2 The relationships between ApEn Value, RR, T_I, T_E, T_{TOT}

A linear plot of ApEn value and RR. A significant negative correlation was observed ($r=-0.79$, $p<0.05$). B linear plot of ApEn value and T_I. A significant positive correlation was observed ($r=0.75$, $p<0.05$). C linear plot of ApEn value and T_E. A significant positive correlation was observed ($r=0.73$, $p<0.05$). D linear plot of ApEn value and T_{TOT}. A significant positive correlation was observed ($r=0.79$, $p<0.05$).

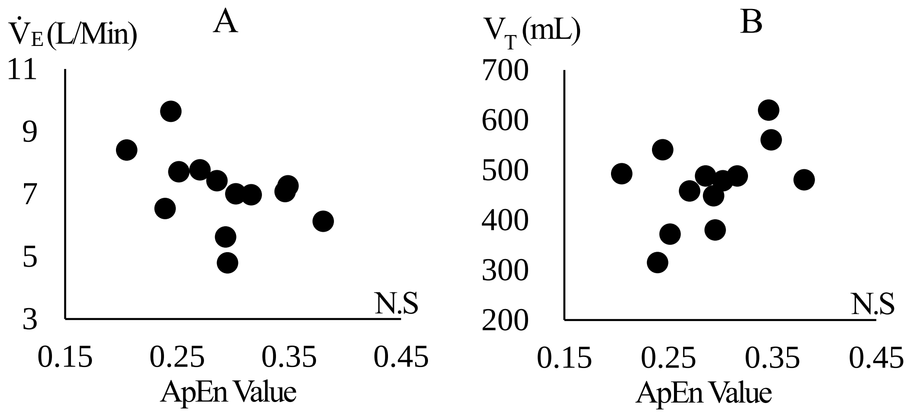

Fig.3 The relationships between ApEn Value, $\dot{V}_E$, V_T

A linear plot of ApEn value and $\dot{V}_E$. No significant correlation was observed. B linear plot of ApEn value and V_T. No significant correlation was observed.

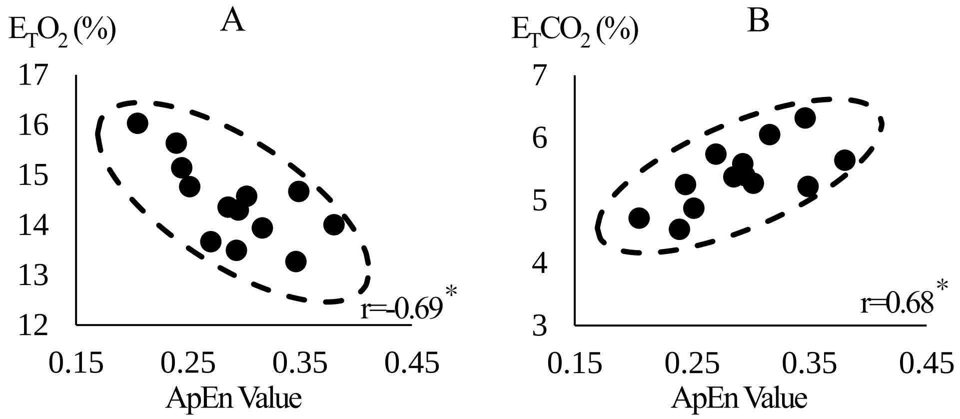

Fig.4 The relationships between ApEn Value, E_TO_2, E_TCO_2

A linear plot of ApEn value and E_TO_2. A significant negative correlation was observed ($r=-0.69$, $p<0.05$). B linear plot of ApEn value and E_TCO_2. A significant positive correlation was observed ($r=0.68$, $p<0.05$).

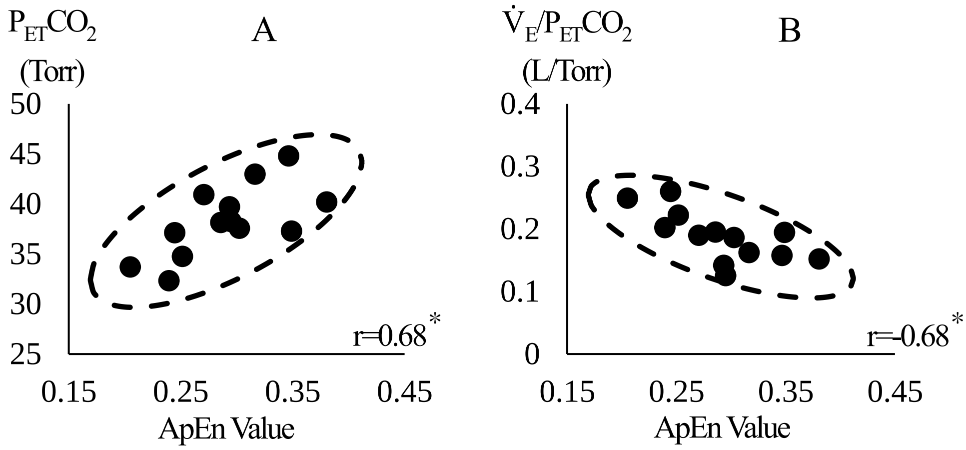

Fig.5 The relationships between ApEn Value, $P_{ET}CO_2$, $\dot{V}_E/P_{ET}CO_2$

A linear plot of ApEn value and $P_{ET}CO_2$. A significant negative correlation was observed ($r=0.68$, $p<0.05$). B linear plot of ApEn value and $\dot{V}_E/P_{ET}CO_2$. A significant positive correlation was observed ($r=-0.68$, $p<0.05$).

呼吸波形の規則性は換気パラメータに依存する

Ⅰ．緒言

呼吸は1日に約20000回行われる生命活動において重要な行動である．呼吸の主な機能は生命を維持するために酸素を吸い込み，二酸化炭素を吐き出すことであることは広く知られている．この生命を維持するための呼吸は代謝性呼吸と呼ばれていて脳幹の延髄と橋にある呼吸中枢で発生する．しかし呼吸には代謝性呼吸に加え脳の上部中央で発生する行動性呼吸が存在する[1,2]．行動性呼吸は代謝性呼吸と異なり意識的に変動させることが可能な呼吸であり，発音や深呼吸などがこれに当たる．近年，この行動性呼吸のうち様々な感情の影響を受ける情動性呼吸に関する報告がなされている[2]．情動性呼吸の中枢は辺縁系の扁桃体にあり[3,4]，幸福や悲しみ，恐怖などの感情の変化に対して応答している．つまり呼吸はホメオスタシスの維持を主とする代謝性呼吸に加え，意識的に変動させることが出来る行動性呼吸や感情の変化に応答する情動性呼吸によって生成，維持され常に複雑な変動をする．

生体信号の時系列データは様々な要因により変動することが知られている．このような時系列データの特徴を検討する際，データの平均値や標準偏差では判別が困難なため，非線形的な手法を用いることが望ましい[5]．システムの規則性や秩序性を定量化する非線形的な手法にエントロピーがある．エントロピーは元来熱力学から生まれたものであり，現在では統計力学や情報倫理など様々な分野で用いられている．エントロピーのうちApproximate Entropy(ApEn)は，Pincusが臨床生理学分野において経時的なデータの複雑さを定量化するために開発した指標である[5]．これまでApEnを用いた研究報告は多く，Pincusら[6]は乳児突然死症候群(SIDS)の心拍変動の規則性を検討しており，SIDSで亡くなった乳児の心拍数は正常範囲にあるにもかかわらず，健康な乳児に比べ規則的であることを報告している．Ryanら[7]は加齢とともに心拍変動が規則的になり，男性は女性よりも規則的であることを報告している．Shinら[8]は心房細動の自然発作前に心拍変動が規則的に変化することを明らかにしている．これらの報告からApEnは心拍変動の規則性を定量化することができる手法であり，疾病や加齢に伴って心拍変動が規則的に変化していくことが明らかとなっている．心拍変動と同様に呼吸も複雑な変動をする生体信号である．そのためApEnを用いて呼吸波形の規則性を評価することが可能であると考える．しかしながらApEnを呼吸解析に用いた報告は少なく，呼吸波形において規則性が存在するのか明確でない[9,10,11]．
我々は健常成人を対象に安静状態において連続した呼吸波形に規則性が存在するのか，換気パラメータとどのような関係性を示すのか明らかにすることを目的として測定を行った．

Ⅱ．対象と方法

１．対象

対象者は健常成人大学生13名(男性8名，女性5名)である．選定には呼吸器疾患の無い者とした．対象者の年齢は21.0±0.7歳(平均値±標準偏差)，身長は163.1±8.4cm，体重は57.1±11.6kgであった．対象者には本研究の趣旨を十分に説明したのち，文書にて同意を得た．また本研究は東京有明医療大学倫理審査委員会の審査，承認(承認番号：有明医療大倫理承認第287号)を得て実施された．

２．方法

１）呼吸代謝の測定

呼気ガス分析器(AE-100i, Minato Medical; Osaka, Japan)に接続されたフェイスマスクを対象者に装着した状態で坐位安静時呼吸代謝の測定を5分間行った．測定は室温26.79±0.72℃に維持された静かな室内で行われた．呼気ガス分析器から呼吸数(RR)，一回換気量(V_T)，分時換気量($\dot{V}_E$)，呼気終末酸素濃度(E_TO_2)，呼気終末二酸化炭素濃度(E_TCO_2)，呼気終末二酸化炭素分圧($P_{ET}CO_2$)，吸気時間(T_I)，呼気時間(T_E)，呼吸時間(T_{TOT})を抽出した．またCO_2に対する感受性の指標として$\dot{V}_E/P_{ET}CO_2$の算出を行った．呼気ガス分析器から得られたこれらのデータは，測定中5分間の平均値を解析対象とした．

２）呼吸波形の取得

呼気ガス分析器からFlow波形をA/Dコンバーター(PowerLab, ADInstruments; Sydney, Australia)を介して，ノートPCに入力し，解析ソフトウェア(LabChart7，ADInstruments)にて記録を行った．記録された5分間のFlow波形のうち，体動などのアーチファクトの無い10波形を5ヶ所から任意に選定し，それぞれのApEnを算出した．なお解析には5ヶ所のApEnの平均値を用いた．

３）ApEn値の算出

ApEnは時系列データに含まれる波形数およびデータ数の影響を受けるため，算出する際には，選定されたデータ間で波形数およびデータ数を統一する必要がある[12]．そのため本研究では，波形数を10呼吸分のFlow波形とし，MATLAB7(MathWorks; Natick, MA)にて，3次スプライン補間を用いてデータ数を1500に再サンプリングしデータ数の統一を行った．またApEn値を算出する際には，ベクトル空間を決定するmと，ノイズの影響をさける役割であるrを設定する必要があり，本研究では阿部ら[12]の報告を参考に$m = 2$，$r = 0.15SD$とした．ApEn値の算出式は以下に示す．

$$ApEn(m, r, N) = \phi(m, r, N) - \phi(m + 1, r, N)$$

ApEn値の下限値は0であり，サインカーブのような規則正しい時系列データのApEn値は0に近い値を示し，逆に規則性の無い乱雑な時系列データは高値を示す．本研究のApEn値算出の設定ではサインカーブ(0.25Hz)のApEn値は0.181であり，表計算ソフト(Microsoft Office Excel, Microsoft; Redmond, WA)で作成した一様乱数のApEn値は1.360であった(Fig.1).

３．統計処理

測定データは平均値±標準偏差にて表記した．JMP Pro 14 (JMP Pro14.2.0, SAS Institute; Cary, NC)にて，呼吸波形のApEn値と各換気パラメータの関係をPearsonの積率相関係数を用いて検討した．危険率5%未満を有意とした．

Ⅲ．結果

対象者の呼吸波形の ApEn 値は 0.291±0.050 であった．各換気パラメータの平均値は Table.1 に示す．以下に呼吸波形の ApEn 値と換気パラメータの関係について示す．

1）呼吸数との関係

呼吸波形の ApEn 値と RR は負の相関を認めた(Fig.2-A)．また T_I，T_E，T_{TOT} と正の相関を認めた(Fig.2-B,C,D)．これは，1 回あたりの呼吸時間が短く，1 分間当たりの呼吸回数が多い者は呼吸波形の規則性が高いことを示している．

2）換気量との関係

呼吸波形の ApEn 値と V_T，$\dot{V}_E$ とは有意な相関関係を認めなかった(Fig.3)．

3）呼気終末ガス濃度との関係

ApEn 値と E_TO_2 は負の相関を，ApEn 値と E_TCO_2，$P_{ET}CO_2$ とは正の相関を認めた(Fig.4)．これは，呼気終末の O_2 が高く，CO_2 が低いものは呼吸波形の規則性が高いことを示している．

4）CO_2 の感受性との関係

ApEn 値と $P_{ET}CO_2$ とは正の相関を認め，$\dot{V}_E/P_{ET}CO_2$ とは負の相関を認めた(Fig.5)．これは CO_2 の感受性が高い者は呼吸波形の規則性が高いことを示している．

Ⅳ．考察

1）呼吸波形の ApEn 値

対象者の呼吸波形の ApEn 値は 0.291±0.014 であった．ApEn 値は算出設定によって変動するため，あくまでも得られたデータ間の相対的な差であり，規則性の絶対値で検討するものではない [12]．本研究で得られた呼吸波形はサインカーブ(0.181)より乱雑で，一様乱数(1.360)よりも規則的であったことから，呼吸波形にはある程度の規則性が存在した．心拍変動の規則性に関して，加齢により規則的なものに変化すると報告されている [6,7]．また加齢によって自律神経活動が低下することで，心拍変動係数が直線的に低下する [13]ことが報告されている．生体応答の時系列データが規則的な様相を示す場合，外乱の影響を受けにくい固有な状態である可能性があり，規則性の高い呼吸波形は，外乱の影響を受けにくい呼吸状態であると考える．

2）呼吸波形の規則性と呼吸数，呼気終末ガス濃度

本研究で得られた主な知見として，呼吸数が多い者の ApEn 値は低値を示し，呼吸数が少ない者の ApEn 値は高値を示すことが明らかとなった．このことは，呼吸数の多い者の呼吸波形は規則的なものであることを意味している．呼吸数が多い場合は呼吸時間が短く，呼吸数が少ない場合は呼吸時間が長くなる．分時換気量が一定で，呼吸数が多く呼吸時間が短い場合，一回換気量が少ないことを意味する．分時換気量が一定で一回換気量が少ないと一回の換気で占める死腔量の割合が増加し，肺胞換気量が低下する．死腔量が増加することで，ガス交換に関与しない酸素が呼気終末に増加する．つまり本研究において呼気終末 O_2 濃度が高値を示した者，呼気終末 CO_2 濃度が低値を示した者の呼吸波形の規則性が高かったことは呼吸数が多いことが影響していると考える．また呼吸波形の規則性と分時換気量と一回換気量の間には有意な相関関係を認めなかった．このことから，呼吸波形の規則性を決定する要素には換気量でなく，呼吸数，呼吸時間の影響が強いことが明らかとなった．

3）呼吸波形の規則性と CO_2 の感受性

$P_{ET}CO_2$ と動脈血二酸化炭素分圧は極めて近似しており，2つの値はほとんど等しいという仮説に基づき $P_{ET}CO_2$ は動脈血二酸化炭素分圧を推察するパラメータとして用いられている．$P_{ET}CO_2$ が上昇すると低換気状態，低下すると過換気状態であることを示す．本研究において $P_{ET}CO_2$ が低値を示した者の呼吸波形が規則的であったことから，過換気状態に近い呼吸を行う場合の呼吸波形は規則的なものになる可能性を示唆した．$\dot{V}_E/P_{ET}CO_2$ は呼吸中枢の CO_2 に対する感受性として用いられる指標であり，板倉ら[14]は閉鎖回路再呼吸法にて過換気症候群患者の $\dot{V}_E/P_{ET}CO_2$ は，非発作時においても健常者に対して高値を示したと報告している．また過換気症候群患者は CO_2 再呼吸時に一回換気量でなく呼吸数を増加させ換気量の増加を行っていたと報告している．本研究において $\dot{V}_E/P_{ET}CO_2$ が高値を示し，CO_2 の感受性が高い者の呼吸波形は規則的であることが明らかとなった．一般的に過換気症候群は過呼吸症候群ともいわれ，不安によって引き起こされた換気発作によって動脈血二酸化炭素分圧の低下，pH の上昇による呼吸性アルカローシス，交感神経機能亢進などが生じ，全身に多彩な身体症状を呈する．過呼吸は過度なストレス状況において徐々に呼吸が速くなる．空気を十分に吸い込めない息苦しい感覚を抱くため，より多くの空気を吸い込もうと呼吸はさらに速くなっていく．その結果生じたしびれなどの身体症状は不安を増大させ，さらに過呼吸が進行するという悪循環に陥る．つまり過換気状態と不安は密接に関わっていると考えられ，本研究において呼吸波形が規則的な者は呼吸数が多く，CO_2 の感受性が高まり，過換気状態に近い呼吸を行っていたことから無意識的に息苦しさや不安を感じていた可能性が推察された．

4）呼吸と不安感の関係性

個人の不安度と呼吸数に関して Kato ら[15] は安静状態において呼吸数が増大している者は高い不安状態であったと報告している．不安によって呼吸数が増大するのは，呼吸調節機構のうち扁桃体を中枢とする情動性呼吸が関与しているとされている[3,4]．また過換気症候群患者やパニック障害患者は，不安状態が高く，呼吸回数が増加し，動脈血および肺胞の CO_2 濃度の低下が持続することがよく知られている[13]．本研究においても呼吸数が多く，過換気状態に近い呼吸を行っていた者の ApEn 値が低値を示したことから，情動が何らかのネガティブな状態にある者は情動性呼吸の関与によって呼吸波形の規則性が高まった可能性が考えられた．規則性が高くなるということは，律動的な呼吸となり呼吸のために用いられるエネルギーの損失を防ぐ可能性がある．しかし，浅く速い呼吸は死腔量が増大し，肺胞換気量を低下させるため，実質的な換気効率の観点からは非効率的な換気状態である．例えば運動時においては，動作時間や負荷に伴って呼吸数と一回換気量が増大することで，死腔換気率(死腔量/一回換気量)を低下させる[17]．また歩行や走行，自転車運動など一定の周期で連続して実施される運動を行う際，呼吸数や呼吸の周期が運動の周期に影響を受け，運動リズムと呼吸リズムの同期(Locomotor Respiratory Coupling : LRC)が生じることが知られている[18,19]．この LRC は酸素摂取量の低下[20]や呼吸困難感の軽減[21]などの効果が示されており，運動動作に伴った呼吸数の増加は，運動中の換気効率を向上させるために重要である．これら運動中の呼吸応答の場合，呼吸数の増加は妥当であるが，本研究は安静時の測定である．安静状態でありながら呼吸数が多い者は，無意識的に息苦しさを感じ，外乱の影響を受けにくい律動的な呼吸を行うことで呼吸に伴うエネルギー損失を防ごうとしている可能性が推察された．

これらのことから，呼吸波形の規則性は換気パラメータのうち呼吸数，呼気終末ガス濃度と関係している可能性を認めた．また安静時において息苦しさや不安感を感じることで，波形の規則性が高い呼吸すなわち外乱の影響を受けにくい律動的な呼吸となる可能性を示唆した.

V．結論

13名の安静呼吸状態での換気パラメータと呼吸波形の規則性について検討した結果，呼吸数と呼吸波形の規則性は密接に関わることが明らかとなり，呼吸数が多く，過換気状態に近づくと，呼吸波形の規則性が高まる可能性を示唆した.

利益相反

本論文に関して，開示すべき利益相反関連事項はない.

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図表

Table 1. 対象者の換気パラメータ

Parameter	Mean	±	SD
RR (BPM)	15.60	±	3.02
V_T (mL)	471.51	±	81.30
$\dot{V}_E$ (L)	7.11	±	1.22
EtO_2 (%)	14.45	±	0.81
$EtCO_2$ (%)	5.39	±	0.50
$P_{ET}CO_2$ (Torr)	38.30	±	3.53
T_I (Sec)	1.60	±	0.34
T_E (Sec)	2.46	±	0.48
T_{TOT} (Sec)	4.06	±	0.77
$\dot{V}_E/P_{ET}CO_2$ (L/Torr)	1.56	±	0.21

Values are mean ± SD

RR, 呼吸数; V_T, 一回換気量; $\dot{V}_E$,分時換気量; E_TO_2,呼気終末 O_2 濃度; E_TCO_2, 呼気終末 CO_2 濃度; $P_{ET}CO_2$, 呼気終末 CO_2 分圧; T_I, 吸気時間; T_E,呼気時間; T_{TOT},1 呼吸時間; $\dot{V}_E/P_{ET}CO_2$,呼吸中枢に対する CO_2 の感受性.

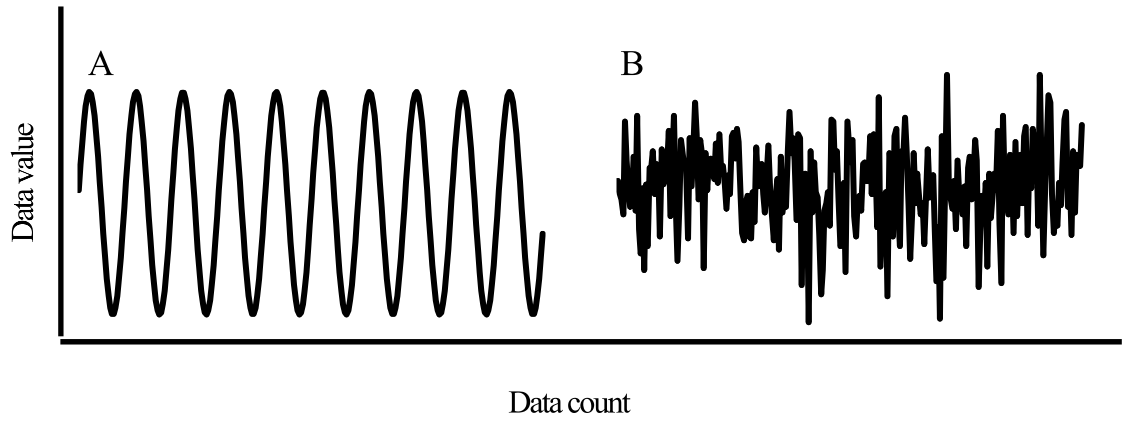

Fig1. サインカーブ(A)と一様乱数データ(B)の ApEn 値.

サインカーブの ApEn 値は 0.181 であり， 一様乱数データの ApEn 値は 1.360 であった.

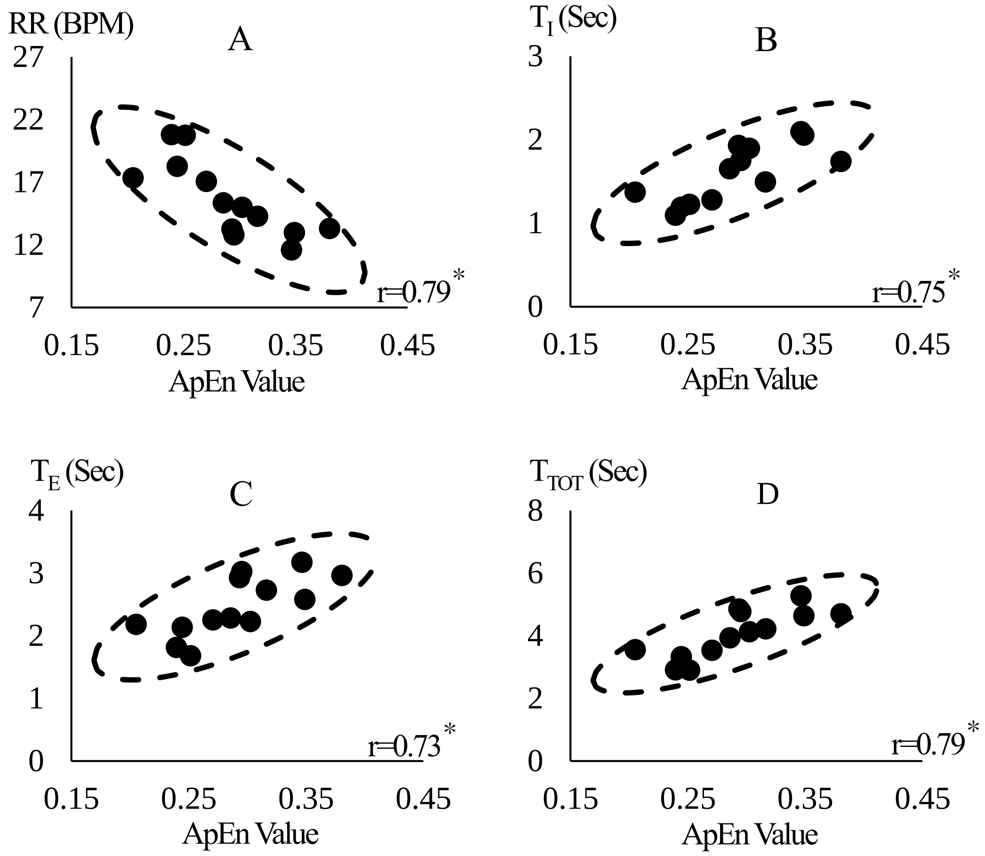

Fig.2 呼吸波形の ApEn 値と呼吸数と呼吸時間の関係

A；呼吸波形の ApEn 値と呼吸数の間に有意な負の相関を認めた(r=-0.79, p<0.05).

B；呼吸波形の ApEn 値と吸気時間の間に有意な正の相関を認めた(r=-0.79, p<0.05).

C；呼吸波形の ApEn 値と呼気時間の間に有意な正の相関を認めた(r=0.73, p<0.05).

D；呼吸波形の ApEn 値と１呼吸時間の間に有意な正の相関を認めた(r=0.79, p<0.05).

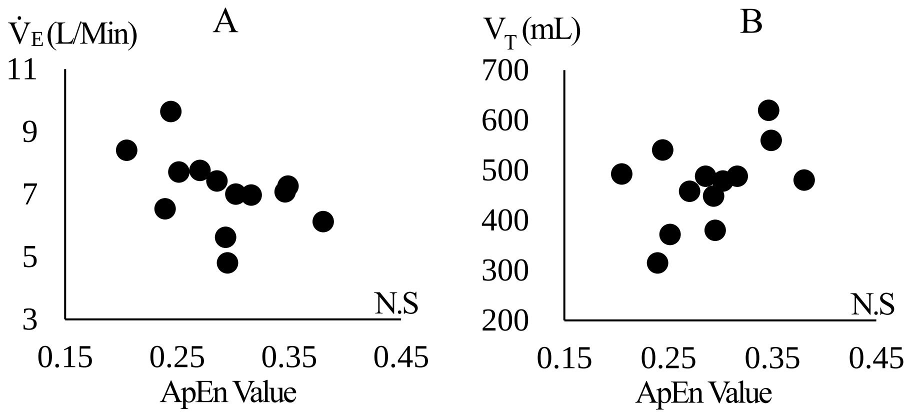

Fig.3 呼吸波形の ApEn 値と分時換気量，１回換気量の関係

A；呼吸波形の ApEn 値と分時換気量の間に有意な相関は認めなかった.

B；呼吸波形の ApEn 値と１回換気量の間に有意な相関関係は認めなかった.

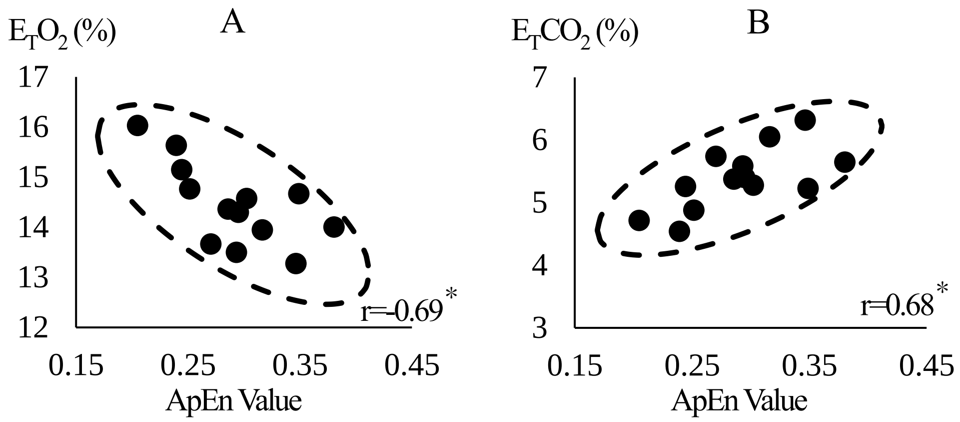

Fig.4 呼吸波形の ApEn 値と呼気終末ガス濃度の関係

A；呼吸波形の ApEn 値と呼気終末 O_2 濃度の間に有意な負の相関を認めた($r=-0.69$, $p<0.05$).

B；呼吸波形の規則性と呼気終末 CO_2 濃度の間に有意な正の相関を認めた($r=0.68$, $p<0.05$).

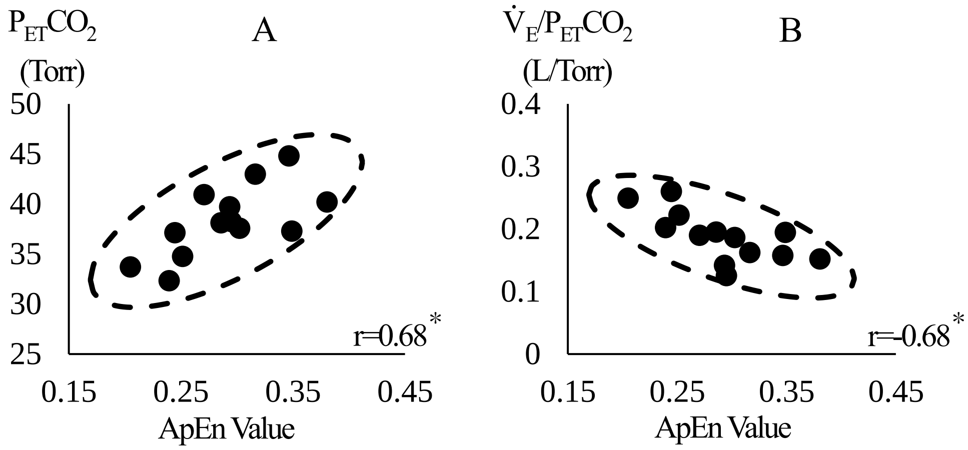

Fig.5 呼吸波形の規則性と呼気終末 CO_2 分圧，呼吸中枢の CO_2 感受性の関係

A；呼吸波形の ApEn 値と呼気終末 CO_2 分圧の間に有意な正の相関を認めた($r=0.68$, $p<0.05$).

B；呼吸波形の ApEn 値と呼吸中枢の CO_2 感受性の間に有意な負の相関を認めた($r=-0.68$, $p<0.05$).

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